REMARKS/ARGUMENTS

Applicants' counsel thanks the Examiner for careful and thorough examination of the application.

I. FORMAL MATTERS

Applicant acknowledges that the Examiner has withdrawn the prior objection to claims 1-5 and 7-14 because the claims contained the acronym "iscom" in light of applicant's amendment thereto and in light of cancellation of claim 6.

Applicant acknowledges that the Examiner has withdrawn the prior rejection of claims 1, 4-7, and 11-13 under 35 U.S.C. § 112, second paragraph, for indefiniteness, in light of applicant's amendment thereto and in light of cancellation of claim 6.

Applicant acknowledges that the Examiner has withdrawn the prior rejection of claims 11-13 under 35 U.S.C. § 112, first paragraph (written description), in light of applicant's amendment thereto and in light of cancellation of claim 6.

Claims 1, 2, 4, 5, 7, 9, and 10 have been amended and new claims 15-18 have been added. No new matter has been entered. Basis for the amendments can be found in the specification as filed. Regarding claim 1 in particular, support for the limitation "enhancement of an immune response level and an immunomodulating activity" includes disclosure that fraction A of Quil A "in low dose enhance[s] . . . the level of immune responses and the immunomodulatory capacity of other adjuvants in suboptimal doses," Specification as filed (marked "WO 2005/002620" in its header), p. 2, lines 18-20, and "[p]rospective adjuvants are, therefore, often tested together with OVA to show the immune enhancement quantitatively by

measuring level of antibody or qualitatively by measuring the immune modulatory effect," Specification, p. 24, lines 18-20. Support for the limitation "of low toxicity" includes disclosure that fraction A of Quil A "facilitates the use of other adjuvants which, when used by themselves, might be toxic at efficiently high doses," Specification, p. 2, lines 20-21, and that the claims especially relate to "the use of fraction A of Quil A together with one or more other adjuvants where fraction A at a low and well tolerated dose synergistically enhance the immuno enhancing effect of the co administered adjuvant, which by its own is too toxic for prophylactic or clinical use[,] I.e. a low well tolerated (otherwise sub-optimal) dose of the co-administered adjuvant is rendered efficient and feasible for use," Specification, p. 7, lines 8-13. Support for the limitation "the ISCOM particles comprising fraction A of Quil A are less toxic on VERO cells than are QH703 ISCOM matrix particles" includes disclosure that "QWT matrix is less toxic on VERO cells (a monkey cell line) than 703 matrix and C matrix." Specification, p. 4, lines 12-14. Regarding claim 15 in particular, support includes disclosure that "the magnitude of the IgG response . . . should be noted." Specification, p. 5, lines 25-27 and corresponding data in Fig. 8. Regarding claim 5, support includes the following: "[T]he adjuvant fraction A of Quil A, in this text also referred to as QWT and the at least one other adjuvant may be integrated into each one different iscom particle or iscom matrix particles. They may also be integrated into one and the same iscom particle or iscom matrix particles. Thus, the adjuvants may be integrated into each a different iscom particle or different iscom matrix particles and then mixed in a composition." Specification, p. 8, lines 26-31. Regarding claims 16, 17, and 18, support includes the following: "The modulatory effect is e.g. recorded by the capacity to drive antigen specific IgG subclass responses. A response dominated by IgG1 antibody is significant for Th2 while IgG2a is significant for Th1 type of response. A response in both IgG1 and IgG2a implicates the balance

of the immune modulation between Th1 and Th2" Specification, p. 24, lines 20-24. Support for claims 16, 17, and 18 also includes disclosure that "QWT-Matrix with antigen and/or MPL potently enhanced IgG2a antibody response, but also IgG1 indicating a strong balanced immune modulatory effect on the TT antigen in the presence of MPL." Specification, p. 33, lines 27-28.

With regard to new claims 15-18, the dependencies place these claims within the elected claim group I. With regard to the claims that read upon the elected aspects, it is to be appreciated that all of the claims read upon elected species 1 - adjuvant (L) monophosphoryl lipid A and elected species 2 - saponin fraction (A) fraction B. It should be appreciated that although all of the claims do not specifically state monophosphoryl lipid A or saponin fraction B, none of the claims explicitly excludes the presence of monophosphoryl lipid A or saponin fraction B.

The Examiner has objected to claims 1-5 and 7-14 because of the informality that reciting the limitation "another separate ISCOM particles" is contradictory. Applicants have amended claim 1 by deleting "another separate." Accordingly, the objection is respectfully submitted to be overcome.

II. REJECTION OF CLAIMS 1-2, 4-9, AND 14 UNDER 35 U.S.C. § 102(b) – FRIEDE REFERENCE

The Examiner has maintained the rejection of claims 1-2, 4-9, and 14 under 35 U.S.C. § 102(b) as being anticipated by Friede et al., U.S. Pat. No. 6,558,670. Respectfully, as explained below, Friede does not disclose all of the limitations of the claims as currently amended, and thus for at least this reason Friede fails to anticipate the claims. Moreover, as also explained below,

Friede does not disclose all of the limitations arranged or combined in the same way as recited in the claims, and thus for at least this additional reason Friede fails to anticipate the claims.

A. Friede Fails to Disclose All of the Limitations of the Claims as Currently Amended, and Thus for at Least This Reason Friede Fails to Anticipate the Claims

Friede does not disclose all of the limitations of the claims as currently amended, including for example (1) a synergistic effect of low toxicity and (2) immunostimulating complex (ISCOM) particles comprising fraction A of Quil A, wherein the ISCOM particles comprising fraction A of Quil A are less toxic on VERO cells than are QH703 ISCOM matrix particles, among others, and thus does not anticipate the claims. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131.

Claim 1, as currently amended, is directed to the following:

A method of enhancement of an immune response level and an immunomodulating activity comprising intraperitoneally or subcutaneously administering to a subject an effective amount of an adjuvant composition with synergistic effect of low toxicity comprising

immunostimulating complex (ISCOM) particles comprising fraction A of Quil A, and

at least one other adjuvant,

wherein the ISCOM particles comprising fraction A of Quil A are less toxic on VERO cells than are QH703 ISCOM matrix particles, and

the at least one other adjuvant is in free form or integrated into ISCOM particles other than the ISCOM particles comprising fraction A of Quil A.

As can be seen, the claim as amended requires a synergistic effect of low toxicity. A synergistic effect of low toxicity, within the meaning of the claim, is use of an adjuvant at a low and well tolerated dose that synergistically enhances the immuno-enhancing effect of a co-administered adjuvant, which by its own is too toxic for prophylactic or clinical use, such that a low, well tolerated and otherwise sub-optimal dose of the co-administered adjuvant is rendered efficient and feasible for use. This is apparent from the Applicant's disclosure, as noted above, that fraction A of Quil A "facilitates the use of other adjuvants which, when used by themselves, might be toxic at efficiently high doses," Specification, p. 2, lines 20-21, and that the claims especially relate to "the use of fraction A of Quil A together with one or more other adjuvants where fraction A at a low and well tolerated dose synergistically enhance the immuno enhancing effect of the co administered adjuvant, which by its own is too toxic for prophylactic or clinical use[,] I.e. a low well tolerated (otherwise sub-optimal) dose of the co-administered adjuvant is rendered efficient and feasible for use," Specification, p. 7, lines 8-13. The passages of Friede cited by the Examiner (i.e. col. 3, lines 1-5, col. 10, lines 30-60, Example 1, col. 3, lines 25-65, col. 9, lines 30-67, col. 9, lines 50-56, col. 8, lines 60-65, col. 4, lines 9-15, col. 10, lines 65-67, and col. 8, lines 46-54) fail to disclose a synergistic effect of low toxicity within the meaning of the claim, as the passages do not expressly or inherently describe use of an adjuvant at a low and well tolerated dose that synergistically enhances the immuno-enhancing effect of a co-administered adjuvant, which by its own is too toxic for prophylactic or clinical use, such that a low, well tolerated and otherwise sub-optimal dose of the co-administered adjuvant is rendered efficient and feasible for use. Although the cited passages disclose selection of an amount of

protein which induces an immunoprotective response without significant, adverse effects, col. 8, lines 65-67, the reference to protein is as a source of antigen, not as an adjuvant, see, e.g., col. 8, lines 26-31, and thus the disclosure does not thereby disclose the recited synergistic effect of low toxicity within the meaning of the claim. Moreover, to the extent that the cited passages may conceivably disclose use of a non-toxic adjuvant and a co-administered non-toxic adjuvant, such a combination would be incapable of a synergistic effect of low toxicity within the meaning of the claim because the co-administered non-toxic adjuvant, by definition, could not be too toxic for prophylactic or clinical use on its own, and thus the disclosure would not thereby disclose the recited synergistic effect of low toxicity within the meaning of the claim. Accordingly, because the passages of Friede cited by the Examiner fail to disclose a synergistic effect of low toxicity within the meaning of the claim, Friede fails to anticipate claim 1. Moreover, because the remaining claims depend from claim 1, Friede also fails to anticipate the remaining claims.

As can also be seen, claim 1 as amended requires ISCOM particles comprising fraction A of Quil A, wherein the ISCOM particles comprising fraction A of Quil A are less toxic on VERO cells than are QH703 ISCOM matrix particles. The specification states what constitutes fraction A of Quil A relative to the prior art, specifically disclosing in Example 5 the method used by the Applicant to prepare fraction A of Quil A and specifically indicating at page 8, lines 12-22 that the Applicant's method is identical to the method to prepare fraction A of Quil A as described in WO 96/11711, which is of record in this case. Friede cites the same WO 96/11711, among other references, in referring to "fractions of Quil A," specifically regarding adjuvant activity associated with particulate structures, i.e. ISCOMS, "comprising fractions of Quil A," Friede, col. 2, lines 12-17, and regarding "[p]articulate adjuvant systems comprising fractions of Quil A, such as QS21 and QS7," Friede, col. 2, lines 28-30. The passages of Friede cited by the

Examiner, as well as those cited in the immediately preceding sentence, do not specifically disclose fraction A of Quil A, as the term is used in the specification relative to the prior art, let alone ISCOM particles comprising fraction A of Quil A, wherein the ISCOM particles comprising fraction A of Quil A are less toxic on VERO cells than are QH703 ISCOM matrix particles. Of note, "fractions of Quil A," as disclosed in Friede, col. 2, lines 12-17, 28-30, are of course not a specific disclosure of fraction A of Quil A, as would be required for anticipation of the claim. Contrary to the Examiner's apparent position that the applicant is relying on features not recited in the rejected claims in order to distinguish Friede and/or that Applicant seeks to have limitations from the specification read into the claims, Office action dated Dec. 1, 2009, p. 4, Applicant's previous arguments and evidence with regard to fraction A of Quil A, as well as the specification, demonstrate that one of ordinary skill would readily understand from the specification relative to the prior art the meaning of the expressly recited limitation fraction A of Quil A and that the passages of Friede cited by the Examiner fail to disclose fraction A of Quil A. The Examiner's positions that "the Declaration signed by Inventor Karen L[ö]vegren Bengtsson is not commensurate in scope because the claims are not specifically limited a method of intranasal administration Fraction A and C from Quil A," that "[e]venthough Applicant discloses in the Declaration Fraction A and Fraction C of Quil A, said Fractions of A and C do not disclose the materials that make up each fraction and are not materially different than the prior art of Friede et al," and that "the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious," Office action dated Dec. 1, 2009, pp. 4-5, are all directed to obviousness, not anticipation, and thus cannot provide a basis for making or maintaining an anticipation rejection. Accordingly, because the passages of Friede

cited by the Examiner, as well as the passages of Friede cited above, fail to disclose fraction A of Quil A within the meaning of the claim or otherwise, let alone ISCOM particles comprising fraction A of Quil A, wherein the ISCOM particles comprising fraction A of Quil A are less toxic on VERO cells than are QH703 ISCOM matrix particles, Friede fails to anticipate claim 1. Accordingly, also for at least this additional reason, the rejection of claim 1 is respectfully submitted to be overcome. Moreover, because the remaining claims depend from claim 1, Friede again also fails to anticipate the remaining claims, and accordingly the rejection of claims 2, 4-9, and 14 is also again respectfully submitted to be overcome.

B. Friede Also Fails to Disclose All of the Limitations Arranged or Combined in the Same Way as Recited in the Claims, and Thus for at Least This Additional Reason Friede Fails to Anticipate the Claims

Friede also does not disclose all of the limitations arranged or combined in the same way as recited in the claims, e.g. a method comprising the specifically recited administration of the specifically recited composition, and thus for this additional reason also fails to anticipate the claims. "[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." Net Moneyin, Inc. v. Verisign, Inc., 545 F.3d 1359, 1371 (Fed. Cir. 2008) (emphasis added); see also Ex parte Frye, Appeal 2009-006013 (B.P.A.I. 2010), at 11) ("To establish anticipation, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." (emphasis added)). In this regard, anticipation requires that a reference "must clearly and unequivocally disclose the

claimed [subject matter] or direct those skilled in the art to the [subject matter] without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." In re Arkley, 455 F.2d 586, 587 (C.C.P.A. 1972).

The passages of Friede cited by the Examiner fail to disclose all of the limitations arranged or combined in the same way as recited in the claims. Specifically, the passages do not clearly and unequivocally disclose the method of claim 1, because, for example, the passages do not disclose any method comprising intraperitoneally or subcutaneously administering to a subject an effective amount of any specific adjuvant composition, let alone an adjuvant composition comprising ISCOM particles and at least one other adjuvant, as required by claim 1, and also because the passages do not disclose any adjuvant composition, as recited, including ISCOM particles comprising any specific saponin(s), let alone fraction A of Quil A, as required by claim 1. The passages also do not direct those skilled in the art to the method of claim 1 without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference, because, for example, the passages cited are related as a series of generic disclosures regarding different aspects of potential compositions, potential methods of use, and potential purposes of use of the vaccine adjuvants disclosed by Friede, e.g. disclosure of (1) methods of treatment and methods of inducing a systemic antigen-specific immune response, col. 3, lines 1-5; (2) uses for prophylactic and therapeutic purposes and as a medicament, col. 10, lines 30-60; (3) a sole specific example involving intranasal administration, not intraperitoneal or subcutaneous administration as required by the claim, and involving an adjuvant composition including free saponin, not ISCOM particles as required by the claim, Example 1; (4) combinations of saponin and CpG to form vaccines that may be administered via the systemic or mucosal route, col. 3, lines 25-65; (5) adjuvants or vaccines

including CpG and saponin that may be separate or associated, for example via a carrier such as aluminium hydroxide or by a cationic liposome or ISCOM, col. 9, lines 30-67; (6) enteric formulations, suppositories, or transdermal or transcutaneous delivery formulations, col. 8, lines 60-65; (7) saponins corresponding to Quil A and fractions thereof, including QS21, QS7, and QS17, col. 4, lines 9-15; and (8) administering a vaccine through a systemic route, such as intramuscular or subcutaneous administration or by a mucosal route, such as the oral/alimentary or nasal route, col. 8, lines 46-54. It would not be plausible to contend that the series of generic disclosures regarding different aspects of the compositions, methods of use, and purposes of use of the vaccine adjuvants disclosed by the passages of Friede cited by the Examiner could direct those skilled in the art to the method of claim 1 without any need for picking, choosing, and combining the various disclosures. Because the passages cited by Friede do not clearly and unequivocally disclose the method of claim 1 or direct those skilled in the art to the method of claim 1 without any need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference, the passages cited do not disclose all of the limitations arranged or combined in the same way as recited in the claim. Accordingly, for at least this additional reason too, the rejection of claim 1 is respectfully submitted to be overcome. Moreover, because the remaining claims depend from claim 1, Friede also fails to anticipate the remaining claims, and accordingly the rejection of claims 2, 4-9, and 14 is also respectfully submitted to be overcome.

III. REJECTION OF CLAIMS 1-5 AND 7-14 UNDER 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 1-5 and 7-14 under 35 U.S.C. § 103(a) as being unpatentable over Friede in view of Cox et al (WO 96/11711). Respectfully, as

explained below, the Examiner has not explained all of the differences between Friede in view of Cox and the claims, and thus for at least this reason Friede in view of Cox fails to render obvious the claims. Moreover, as also explained below, Friede in view of Cox would not have provided a reasonable expectation of success with regard to achieving the claimed methods, and thus for at least this additional reason too Friede in view of Cox fails to render obvious the claims.

A. The Examiner Has Not Explained All of the Differences Between Friede in View of Cox and the Claims, and Thus for at Least This Reason Friede in View of Cox Fails to Render Obvious the Claims

The Examiner has not explained all of the differences between Friede in view of Cox and the claims, for example regarding the synergistic effect of low toxicity, as recited in claim 1, and thus Friede in view of Cox fails to render obvious the claims. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious." MPEP § 2141, III. In this regard, "Office personnel must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art." Id.

At least one difference exists between the prior art and the method of claim 1, namely that the method of claim 1 includes the limitation of a synergistic effect of low toxicity, i.e. use of an adjuvant at a low and well tolerated dose that synergistically enhances the immuno-enhancing effect of a co-administered adjuvant, which by its own is too toxic for prophylactic or clinical use, such that a low, well tolerated and otherwise sub-optimal dose of the co-administered adjuvant is rendered efficient and feasible for use, whereas the prior art cited does not. Specifically, as can be seen, claim 1 as currently amended includes the limitation of a

synergistic effect of low toxicity. For the reasons indicated above, the passages of Friede cited by the Examiner (i.e. col. 3, lines 1-5, col. 10, lines 30-60, Example 1, col. 3, lines 25-65, col. 9, lines 30-67, col. 8, lines 60-65, col. 4, lines 9-15, Abstract, col. 10, lines 65-67, col. 8, lines 46-54) fail to disclose a synergistic effect of low toxicity within the meaning of the claim. The passages of Cox cited by the Examiner (i.e. page 3, lines 20-30, pages 4-5, pages 9-24, page 7, line 24, page 1, Table 1 on page 8) also fail to disclose a synergistic effect of low toxicity within the meaning of the claim.

In this regard, the Examiner has not explained why the difference of a synergistic effect of low toxicity, within the meaning of the claim, would have been obvious. Although the Examiner contends that "one skilled in the art would be motivated to use the ISCOM matrix complex (as disclosed by Cox et al) as the ISCOM particle as taught by Friede et al in order to take advantage of the reduced Quil A toxicity associated with the use of said complexes," Office action dated Dec. 1, 2009, p. 8, that is not an explanation of the difference between Friede in view of Cox and the claim regarding a synergistic effect of low toxicity, because one could take advantage of reduced Quil A toxicity in general consistent with the teachings of Friede in view of Cox without seeking or obtaining a synergistic effect of low toxicity in particular within the meaning of the claim, and thus a general motivation regarding taking advantage of reduced Quil A toxicity does not imply a specific motivation regarding a synergistic effect of low toxicity. Because the Examiner has not explained this difference between the prior art and the method of claim 1 in this regard, the Examiner has not clearly articulated any reason why the claimed method would have been obvious over Friede in view of Cox. Accordingly, Friede in view of Cox fails to render claim 1 obvious. Accordingly, for at least this reason, the rejection of claim 1 is respectfully submitted to be overcome. Moreover, because the remaining claims depend from

claim 1, Friede in view of Cox also fails to render the remaining claims obvious, and accordingly the rejection of claims 2-5 and 7-14 is also respectfully submitted to be overcome.

B. Friede in View of Cox Also Would Not Have Provided a Reasonable Expectation of Success with Regard to Achieving the Claimed Methods, and Thus for at Least This Additional Reason Too Friede in View of Cox Fails to Render Obvious the Claims

Friede in view of Cox also would not have provided a reasonable expectation of success with regard to achieving the method of claim 1, for example regarding obtaining a synergistic effect of low toxicity, as required by the claims, and thus for at least this additional reason Friede in view of Cox fails to render obvious the claims. "Obviousness does not require absolute predictability, however, at least some degree of predictability is required." MPEP § 2143.02, II. In this regard, "[e]vidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." Id.

One of ordinary skill would not have had a reasonable expectation of success with regard to practicing the method of claim 1, including the limitation of a synergistic effect of low toxicity, based on any arguments presented by the Examiner regarding Friede in view of Cox or otherwise. It has long been appreciated by those of skill in the art that the results of combining adjuvants for use in a single composition are highly empirical, not reasonably predictable. This is demonstrated, for example, in LaValle, 171 Journal of Immunology 2384, 2384 (2003), which is of record and which discloses with regard to CT and LPS, both of were well known and well studied adjuvants, that combining the two for use in a single composition resulted in a complicated mix of synergistic effects and inhibitory effects, specifically that "CT synergized with low doses of LPS to induce IL-10 production by immature DC [i.e. dendritic cells]" and

"enhanced the expression of CD80, CD86, and OX40 (CD134) on DC and induced the secretion of the chemokine, macrophage inflammatory protein-2 (MIP-2), but inhibited LPS-driven induction of CD40 and ICAM-I expression and production of the inflammatory cytokines/chemokines IL-12, TNF-α, MIP-1α, MIP-1β, and monocytes chemattractant protein-1" thus suggesting "that CT induces maturation of DC, but, by inducing IL-10, inhibiting IL-12, and selectively affecting surface marker expression, suppresses the generation of Th1 cells and promotes the induction of T cells with regulatory activity."

As indicated above, neither the cited passages of Friede nor the cited passages of Cox disclose a synergistic effect of low toxicity within the meaning of the claim. To the extent that Friede expressly discusses synergy, it is in the context that "saponin and oligonucleotides in the adjuvant and vaccine compositions act synergistically in the induction of antigen specific antibody," Friede, col. 3, lines 29-33, that it was "investigated whether lytic saponins such as QS21 and immunostimulants such as CpG were able to enhance in a synergistic fashion systemic immunological responses to an intranasal boosting vaccination of mice," Friede, col. 11, lines 8-11, and that "when both adjuvants [i.e. CpG and QS21] are combined, a synergistic effect on those responses is clearly demonstrated, especially in term of LA2 antibodies," Friede, col. 12, lines 4-7. The Cox reference does not apparently expressly discuss synergy at all. Although the Examiner contends that "[o]ne would have had a reasonable expectation of success because the ISCOM matrix (as disclosed by Cox et al) has been shown to have a significant adjuvant effect and reduced toxicity as well," Office action dated Dec. 1, 2009, for the reasons indicated above, the results of combining adjuvants, even well known and well studied ones, for use in a single composition are highly empirical, not reasonably predictable. Thus, one of ordinary skill, appreciating the lack of reasonable predictability regarding the effects of combining adjuvants

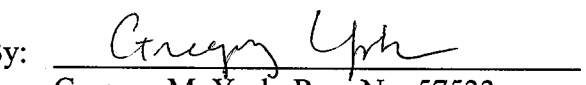
for use in a single composition would have had no reasonable expectation of success regarding practicing the method of claim 1, including the limitation of a synergistic effect of low toxicity. Accordingly, Friede in view of Cox fails to render obvious claim 1. For at least this additional reason, the rejection of claim 1 is therefore respectfully submitted to be overcome. Moreover, because the remaining claims depend from claim 1, Friede in view of Cox also fails to render the remaining claims obvious, and accordingly the rejection of claims 2-5 and 7-14 is also respectfully submitted to be overcome.

IV. REQUEST THAT APPLICATION BE ALLOWED

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in a condition for allowance, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge the same to our Deposit Account No. 16-0820, our Order No. ALBI-46419.

Respectfully submitted,
PEARNE & GORDON, LLP

By: 
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